

PATENT SPECIFICATION

768,089

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Date of Application and filing Complete Specification: March 23, 1954.

No. 8511/54.

Application made in Germany on March 30, 1953.

Complete Specification Published: Feb. 13, 1957.

Index at acceptance:—Class 2(3), C2(A2: B21: B38: T21).

International Classification:—C07c, d.

COMPLETE SPECIFICATION

Di-Guanyl Hydrazones

We, **FARBENFABRIKEN BAYER AKTIEN-GESELLSCHAFT**, a body corporate organised under the laws of Germany of Leverkusen, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to di-guanyl-hydrazones. The invention more particularly relates to and has as its object, the production of di-guanyl-hydrazones of di-phenyl di-aldehydes or di-phenyl di-ketones which have been found to exhibit valuable therapeutic properties.

The new compounds, in accordance with the invention, are di-guanyl-hydrazones of a di-phenyl di-aldehyde or di-phenyl di-ketone, in which the phenyl nuclei are joined either through an —O—R—O— radical having up to 12 atoms in which R is a divalent aliphatic radical, or through an oxygen atom, or through an —O—R—O—R—O— radical having up to 12 atoms in which R is a divalent aliphatic radical, or are directly linked to each other.

The term "guanyl radical" is intended to include unsubstituted guanyl radicals and substituted guanyl radicals in which 1 to 3 of the hydrogen atoms are substituted with alkyl, aryl or aralkyl radicals. The term is also intended to include guanyl radicals in which the 2 nitrogen atoms are incorporated into a hetero-

cyclic ring. The C=N—NH—Y group may be at the 2, 3, 4, 5 or 6 position, i.e., the compounds may be *ortho*, *meta* or *para* com-

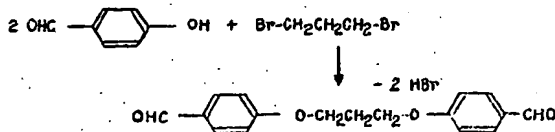
pounds.

These new compounds have been found to exhibit an extremely high bactericidal activity and have been found particularly potent against a number of bacteria as, for example, streptococci, enterococci, pneumococci and staphylococci, so that the compounds are excellently suited as disinfectants for internal and external purposes. Due to their excellent compatibility, they are extremely well suited as oral disinfectants.

The new compounds, in accordance with the invention, may be prepared by a condensation reaction between an amino guanidine and a di-phenyl di-aldehyde or di-phenyl di-ketone, as defined above.

The di-aldehydes and di-ketones employed in the condensation reaction may be prepared in various manners depending upon the nature of the bridging member between the phenyl nuclei. Thus, for example, di-phenyl-4,4'-di-aldehyde and di-phenyl ether-4,4'-di-aldehyde, may be obtained from the respective di-methyl compounds by oxidation or through the tetrahalomethyl compounds as described in the literature.

Di-phenol-di-aldehyde and di-ketones in which the phenyl groups are saturated by —O—R—O— or —O—R—O—R—O— bridges are easily obtainable by condensing hydroxy benzaldehydes or hydroxy benzo-ketones with alkyl di-halides in the presence of alkali metal hydroxides. This reaction in connection with 4-hydroxybenzaldehyde and 1,3-dibromopropane may be represented as follows:

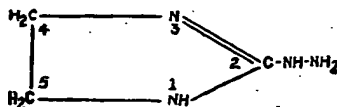


Two mols of the amino guanidine are condensed with a mol of the di-aldehyde or di-ketone to give the —O—R—O— type bridge. The amino guanidines may be unsubstituted

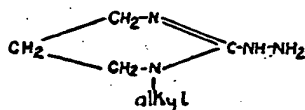
or may be substituted in any manner provided that the hydrazino group remains intact, and, if necessary, be converted to the desired end products after the reaction. One to three

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hydrogen atoms of the amino guanidino which are not attached to the hydrazine group may be substituted by alkyl, aryl or aralkyl radicals, to give the correspondingly substituted hydrazone derivatives. Thus, for example, alkyl, di-alkyl or tri-alkyl amino guanidines may be used. The amino guanidines may also contain two nitrogen atoms of the guanidine configuration incorporated in a heterocyclic ring as, for example, 2-hydrazino-2-imidazoline of the formula:



Or a 2-hydrazino - 1,4,5,6 - tetrahydropyrimidine of the formula:



As examples of aromatic amino guanidines which may be used there may be mentioned mono-, di- and triarylamino guanidines containing a free hydrazino, i.e. $-\text{NH}-\text{NH}_2$ group as, for example, phenyl- or di-phenyl aminoguanidine. In addition, amino guanidines which are substituted by mixed aliphatic aromatic radicals such as N-ethyl-N-phenyl amino guanidine containing a free hydrazino group may be used. The amino guanidine may also be incorporated in a heterocyclic ring provided that the $-\text{NH}-\text{NH}_2$ remains intact.

These amino guanidines are, for the most part, described in the literature or may easily be obtained according to conventional methods as, for example, by the reduction of nitro guanidines or by the reaction of isothiourea salts and hydrazine. These amino guanidines may also be obtained by reaction of S-alkyl thiosemicarbazide compounds and amines; by the addition reaction of hydrazine and cyanamides or by the desulphurisation of thiourea in the presence of hydrazine.

For the reaction, 2 mols of the same or two different amino guanidines may be reacted with the di-ketone or di-aldehyde. The hydrazino group enters into a condensation reaction with the carbonyl group of the di-aldehydes or di-ketones, splitting off water.

The condensation reaction is preferably effected in an alcoholic or aqueous alcoholic solution or in mixture of water and a water-soluble solvent such as dimethyl formamide and dioxane. The reaction proceeds easily if the compounds are in the form of their salts. The

condensation is preferably effected in the presence of a small excess of acid though it may also be performed in an alkaline medium.

An alternative method for the synthesis of the compounds, in accordance with the invention, consists of first producing the corresponding thiosemicarbazones and thereafter reacting these thiosemicarbazones with ammonia or amines in the presence of heavy metal salts. It is also possible to first produce the corresponding hydrazones and treat the same with cyanamides.

Alternatively, the new compounds may be produced by condensing amino guanidines and benzaldehydes or benzoketones and linking 2 mols of the resulting guanyl hydrazones with a bridging member if such is desired. Thus, for example, *p*-bromobenzaldehyde may be condensed with amino guanidine to yield the guanyl hydrazone of *p*-bromobenzaldehyde which may be converted into the di-guanyl hydrazone of *p,p'*-di-phenyl di-aldehyde.

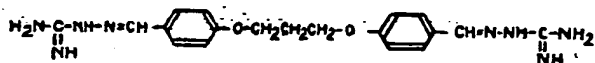
It is also possible to react the condensation products of *p*-hydroxybenzaldehyde and an amino guanidine with a di-halogenoalkane such as di-bromo alkane in the presence of an alkali metal hydroxide thus forming the new condensation products in accordance with the invention.

The salts of the new compounds with strong acids are, for the most part, difficultly soluble in cold water and relatively easily soluble in hot water. They readily yield free bases upon reaction with alkali metal hydroxides or with ammonia. The new compounds are colourless, finely crystallised compounds which yield readily soluble salts with organic acids as, for example, acetic acid and lactic acid.

The following Examples are given for the purpose of illustrating the invention.

EXAMPLE 1.

Fourteen and two tenths grams of *p,p'*-di-aldehyde-1,3-diphenoxypropane (m.p. 126°C .; prepared from hydroxybenzaldehyde and 1,3-dibromopropane in the presence of alkali) are dissolved in 380 ml. of warm alcohol and a solution of 11 grams of amino guanidine hydrochloride, 15 ml of water and 5 ml of concentrated hydrochloric acid is added. The solution is left standing at $60-80^\circ\text{C}$. for 2-3 hours whereupon crystallisation begins. After cooling, the crystals of the dihydrochloride of the m.p. 240°C . are isolated. By dissolution in hot water and precipitation with ammonia, the 4,4'-diguanyl hydrazone of the above aldehyde is obtained as a base. After boiling once for a short time with some ethyl acetate the condensation product is obtained in the form of yellowish-white crystals having a m.p. of 226°C . The compound has the following formula:

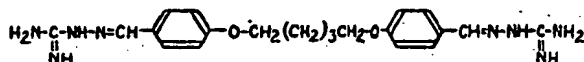


The condensation product can also be obtained from the bis-thiosemicarbazone of the above di-aldehyde (decomposition point 220° C.) by reaction with ammonia and lead oxide in an alcoholic suspension.

EXAMPLE 2.

Thirty one and two tenths grams of *p,p'*-di-aldehyde-1,5-diphenoxy pentane (m.p. 90° C.; prepared from *p*-hydroxy benzaldehyde and 1,5-dibromo-*n*-pentane in the presence of alkali) are dissolved in 250 ml of warm alcohol and reacted with 22 grams of amino guanidine hydrochloride in 25 ml of water with the addition of 10 ml of concentrated

hydrochloric acid. After a violent reaction, the dihydrochloride having a m.p. of 226° C. begins to crystallise after standing for some time at a moderately raised temperature, as described in Example 1. The crystals are isolated and the base is prepared therefrom by dissolution in about 2.5 litres of warm water and precipitation with ammonia. By recrystallising from dilute methanol the diguanyl hydrazone of 4,4'-di-aldehyde-1,5-diphenoxypentane is obtained in fine white crystals having a decomposition point of 240° C. The compound has the following formula:



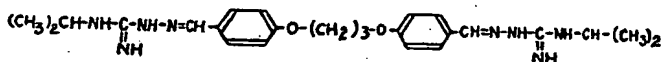
The same compound is obtained by dissolving 5.7 grams of *p*-hydroxybenzaldehyde guanyl hydrazone base (prepared according to Annalen 302, page 304) in 50 ml of absolute alcohol, reacting the same with a solution of sodium ethoxide formed from 0.7 gram of sodium in 22 ml of absolute alcohol and boiling with 3.5 grams of 1,5-dibromo-*n*-pentane for 48 hours. After pouring on ice water with the addition of some ammonia, the reaction product is recrystallised from methanol.

It is further possible to produce the same substance from the bis-thiosemicarbazone of *p,p'*-dialdehyde-1,5-diphenoxypentane (m.p. 210° C.) by reaction with ammonia and lead hydroxide in alcoholic suspension.

EXAMPLE 3.

Fourteen and two tenths grams of *p,p'*-di-

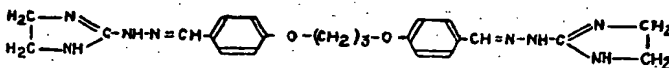
aldehyde-1,3-diphenoxy propane are dissolved in 380 ml of warm alcohol and reacted with 19.7 grams of isopropyl-amino-guanidine-hydrobromide (m.p. 112° C.; prepared from *S*-ethylisopropyl-thiourea-hydrobromide and hydrazine) in 20 ml of water with the addition of some concentrated nitric acid. After prolonged standing with gentle heating, the mixture is poured into 1.5 litres of water with the addition of some ammonia. The precipitated base is suction filtered, dissolved in ammonia and the dihydrochloride of the diguanyl-isopropyl-hydrazone of the above di-aldehyde is precipitated with hydrochloric acid in the form of an oil. The salt crystallises after decanting, washing with water and treating with ethyl acetate. The compound has the following formula:



EXAMPLE 4.

Fourteen and two tenths grams of *p,p'*-dialdehyde-1,3-diphenoxypropane are dissolved in 380 ml of warm alcohol and reacted with 18.1 grams of 2-hydrazino-2-imidazoline hydrobromide (m.p. 186° C.; prepared from 2-ethylmercapto-2-imidazoline hydrobromide and hydrazine) in 18 ml of water with the addition of 5 ml of hydrobromic acid. After

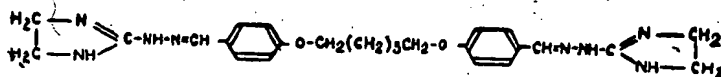
standing on the water bath for one hour, the di-hydrobromide crystallises and is isolated; m.p. 302° C. By dissolution in water and treatment with ammonia and water, the di-imidazolino-hydrazone base of the above aldehyde is obtained after recrystallising from ethanol, the base is obtained in white crystals having a m.p. of 226° C. The compound has the following formula



EXAMPLE 5.

Fifteen and six tenths grams of *p,p'*-dialdehyde-1,5-diphenoxypentane are dissolved in 100 ml of warm alcohol and reacted with 18.1 grams of 2-hydrazino-2-imidazoline hydrobromide in 18 ml of water with the addition of 5 ml of hydrobromic acid. After standing for two hours, the mixture is filtered

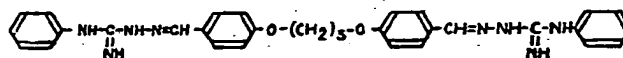
with gentle heat and allowed to crystallise. The di-hydrobromide of the di-imidazolino-hydrazone of the above di-aldehyde is obtained which has a m.p. of 206° C. The base prepared therefrom melts at 232° C. after recrystallising from dilute methanol. The compound has the following formula:



EXAMPLE 6.

Two and eighty four hundredths grams of *p,p'*-dialdehyde-1,3-diphenoxy-propane are dissolved in 75 ml of warm alcohol and reacted with 4.6 grams of phenyl amino guanidine hydrobromide (N^1 -amino- N^2 -phenyl guanidine hydrobromide) (m.p. 111° C.; prepared from *S*-ethyl-*N*-phenyl isothiocurea hydrobromide and hydrazine) in 10 ml of water and 2 ml of hydrobromic acid. After standing for two hours with gentle heating, the mixture is

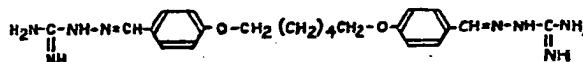
concentrated and cooled. The precipitated dihydrobromide is stirred with concentrated ammonia water and suction filtered. The base is precipitated once more from acetic acid solution with ammonia. The nearly insoluble base of the *p,p'*-di-phenyl guanyldiazone of the above di-aldehyde crystallises from ethyl acetate in yellowish crystals having a decomposition point of 230° C. The compound has the following formula:



EXAMPLE 7.

Sixteen and three tenths grams of *p,p'*-dialdehyde-1,6-diphenoxyhexane are dissolved in 120 ml of warm alcohol and reacted with 11.1 grams of amino guanidine hydrochloride in 11 ml of water with the addition of 5 ml of concentrated hydrochloric acid. The mixture is placed on a water bath and crystallisa-

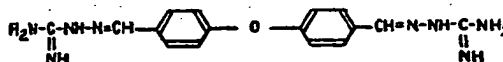
tion soon commences. After standing for two hours with gentle heating, the mixture is cooled and the dihydrochloride having a m.p. of 230° C. is isolated. The base of the di-guanyldiazone of the above di-aldehyde is obtained therefrom in the usual manner and has a m.p. of 242° C. The compound has the following formula:



EXAMPLE 8.

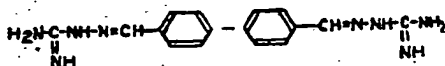
Eleven and three tenths grams of diphenyl ether - 4,4'-di-aldehyde (4,4'-diformyl diphenyl oxide) (prepared from 4,4'-dimethyl di-phenyl ether by tetrabromination and hydrolysis) in 100 ml of alcohol are reacted with 11 grams of amino guanidine hydrochloride in 11 ml of water with the addition of 5 ml of concentrated hydrochloric acid. After standing on a water bath for 3

hours, the mixture is evaporated *in vacuo*. The residue is dissolved in a larger quantity of water and precipitated with ammonia. After recrystallising from methanol and water, the base of the di-guanyl-hydrazone of diphenyl ether-4,4'-di-aldehyde is obtained in white crystals having a decomposition point of 257° C. The compound has the following formula:



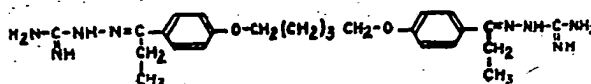
EXAMPLE 9.

Twenty one grams of di-phenyl-4,4'-di-aldehyde (4,4'-diformyl di-phenyl) (prepared from 4,4'-di-methyl di-phenyl by oxidation with chromic acid in a mixture of glacial acetic acid and acetic anhydride) are dissolved in 400 ml of warm alcohol and reacted with 28 grams of amino guanidine carbonate in 53 ml of 4N-hydrochloric acid. After standing on the water bath for 3 hours and cooling the dihydrochloride of the di-guanyl-hydrazone of di-phenyl-4,4'-di-aldehyde is suction filtered and washed. The compound has the following formula:



EXAMPLE 10.

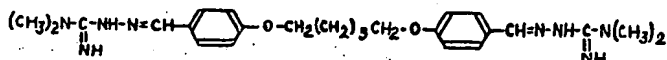
Eighteen and four tenths grams of *p,p'*-di-propionyl-1,5-di-phenoxypentane (m.p. 110° C.; prepared from *p*-hydroxypropionophenone and 1,5-di-bromo-*n*-pentane) in 200 ml of alcohol are reacted with 14 grams of amino-guanidine carbonate in 43 cc of 2.44 N-hydrochloric acid. After standing for a short time on a water bath, the alcohol is substantially evaporated and the residual solution is poured into about 1 litre of water with the addition of ammonia. After filtering and boiling with absolute alcohol, the base is obtained as white crystals having a m.p. of 220° C. Another quantity of this compound crystallises from the alcohol. The compound has the following formula:



EXAMPLE 11.

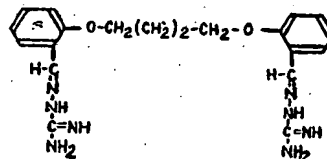
p-Hydroxybenzaldehyde-di-methylguanylhydrazone (m.p. 300° C.; prepared from *p*-hydroxybenzaldehyde and N¹-amino-N³-di-methyl guanidine hydrobromide m.p. 212° C.) are suspended in 200 ml of alcohol and reacted with a solution of sodium ethoxide formed from 1.93 grams of sodium in 60 ml of alcohol. After addition of 4.8 grams of 1,5-

di-bromo-*n*-pentane, the mixture is heated to a boil for 48 hours. After cooling, the mixture is poured into 1 litre of ice water and suction filtered. The di-methyl-guanylhydrazone of *p,p'*-dialdehyde-1,5-diphenoxypentane is obtained as white crystals having a m.p. of 175° C. by recrystallising from methanol and water. The compound has the following formula:



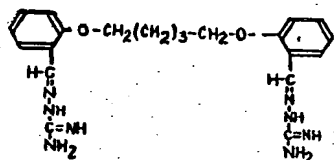
EXAMPLE 12.

Twenty five and eight tenths grams of *o,o'*-di-aldehyde-1,5-diphenoxypentane (melting point 79° C.; prepared from *o*-hydroxybenzaldehyde and 1,5-di-bromo-*n*-pentane in the presence of an alkali metal hydroxide) are dissolved in 160 ml of warm alcohol and reacted with 18.2 grams of amino guanidine hydrochloride in 18 ml of water with the addition of 9 ml of concentrated hydrochloric acid. After heating at about 80° C. for three hours, the mixture is distilled *in vacuo*. The residue is dissolved in about 1 litre of hot water and precipitated with ammonia. By recrystallising from dilute alcohol, the di-guanylhydrazone of 2,2'-di-aldehyde-1,5-di-phenoxypentane is obtained as white crystals having a melting point of 209° C. The compound has the following formula:



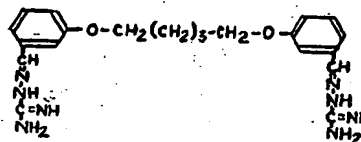
EXAMPLE 14.

Seven grams of *m,m'*-di-aldehyde-1,5-diphenoxypentane (prepared from *m*-hydroxybenzaldehyde and 1,5-dibromo-*n*-pentane in the presence of an alkali metal hydroxide) are dissolved in 25 ml of dry ethanol and reacted with 6 grams of amino-guanidine hydrochloride in 6 ml of water with the addition of 2 ml of concentrated hydrochloric acid. After heating at 70—80° C. for about 3 hours, the liquid portion is distilled off *in vacuo*. The residue is dissolved in hot water and precipitated with ammonia. By recrystallising from dilute methanol, the di-guanylhydrazone of 3,3'-di-aldehyde-1,5-diphenoxypentane having a melting point of 165° C. is obtained as white crystals. The compound has the following formula:



EXAMPLE 13.

Twenty three grams of *o,o'*-dialdehyde-1,4-di-phenoxybutane (melting point 117° C.; prepared from *o*-hydroxybenzaldehyde and 1,4-di-bromo-*n*-butane in the presence of an alkali metal hydroxide) are dissolved in 350 ml of warm, dry ethanol and 17 grams of amino guanidine hydrochloride in 17 ml of water are added. A reaction sets in after the addition of 2 ml of concentrated hydrochloric acid. The mixture is heated at 80° C. for three hours and the liquid portion is distilled off *in vacuo*. The residue is dissolved in hot water and precipitated with ammonia. After recrystallising from about 2 litres of methanol the diguanylhydrazone of 2,2'-di-aldehyde-1,4-di-phenoxybutane having a decomposition point of 228° C. is obtained as white crystals. The compound has the following formula:

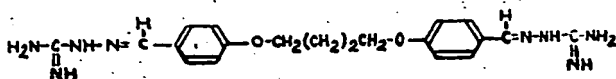


EXAMPLE 15.

Twenty four grams of *p,p'*-di-aldehyde-1,4-di-phenoxybutane (prepared from 4-hydroxybenzaldehyde and 1,4-dibromobutane in the presence of an alkali metal hydroxide) are dissolved in 400 ml of warm alcohol and reacted with 18 grams of amino guanidine hydrochloride in 18 ml of water with the addition of 2 ml of concentrated hydrochloric acid. By heating at 70—80° C. for 3 hours, the dihydrochloride precipitates in fine crystals at elevated temperatures. After cooling, these crystals are dissolved in about 1.5 litres of hot water and the base is precipitated with ammonia. After boiling with methanol,

the di-guanylhyazone of 4,4'-di-aldehydo-1,4-di-phenoxybutane is obtained in white

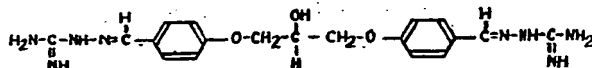
crystals of the decomposition point 255° C. The compound has the following formula:



EXAMPLE 16.

Fourteen grams of *p,p'*-dialdehydo-1,3-di-phenoxypropanol (2) (prepared from *p*-hydroxybenzaldehyde and 1,3 - dibromopropanol) are dissolved in 150 ml of hot alcohol. After addition of 10.3 grams of amino guanidine hydrochloride in 11 ml of water and 5 ml of concentrated hydrochloric acid, the mixture is kept at 70—80° C. for 3 hours whereupon the di-hydrochloride having

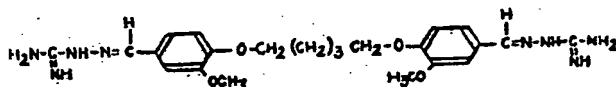
a melting point of 250° C. crystallises gradually. The base is obtained by dissolving the crystals in hot water and precipitating by addition of ammonia. By recrystallising from dilute methanol, the diguanylhyazone of 4,4'-dialdehydo-1,3-di-phenoxypropanol (2) is obtained as white crystals having a melting point of 215° C. The compound has the following formula:



EXAMPLE 17.

Twenty four grams of amino guanidine hydrochloride, dissolved in 24 ml of water with the addition of 8 ml of concentrated hydrochloric acid, are added to an alcohol solution of the di-aldehyde, prepared from 30.4 grams of vanillin and 1,5-dibromo-*n*-pentane in the presence of caustic alkali, and heated at 70—80° C. for three hours. After

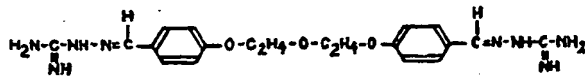
cooling, the di-hydrochloride is isolated and dissolved in a large quantity of hot water and the base precipitated with ammonia. By recrystallising from dilute methanol, the diguanylhyazone of 4,4'-di-aldehydo-2,2'-dimethoxy-1,5'-di-phenoxy-pentane is obtained as white crystals having a melting point of 160° C. The compound has the following formula:



EXAMPLE 18.

Fifteen and seven tenths grams of *p,p'*-dialdehydo-2,2'-diphenoxy diethylether obtained from *p*-hydroxybenzaldehyde, β - β' -di-chloroethylether and sodium hydroxide solution are dissolved in 900 ml of hot ethanol. Eleven grams of amino guanidine hydrochloride in 11 ml of water and 8 ml of concentrated hydrochloric acid are added. The mixture is concentrated to about 150 ml on the water bath. Upon cooling the di-hydrochloride separates.

After recrystallising from a mixture of methanol and ethanol, yellow crystals with a melting point of 187° C. are obtained. After dissolving in water and precipitation in ammonia, the bisguanylhyazone of the *p,p'*-di-aldehydo-2,2'-diphenoxy diethylether is obtained. The base is very difficultly soluble and is purified, by boiling with ethanol, into white crystals, decomposing at 229° C. The compound has the following formula:



What we claim is:—

1. As a new chemical compound, a diguanyl hydrazone of a di-phenyl di-aldehyde or di-phenyl-di-ketone, in which the phenyl nuclei are joined either through an O—R—O radical having up to 12 atoms in which R is a divalent aliphatic radical, or through an oxygen atom, or through an



radical having up to 12 carbon atoms in which R is a divalent aliphatic radical, or are directly linked to each other.

2. A compound according to claim 1, in which the guanyl radicals each have at least 1 hydrogen atom thereof substituted by an alkyl or aryl radical.

3. The di-guanyl hydrazones of diphenyl di-aldehydes or di-ketones hereinbefore specifically mentioned.

4. A process for the production of the diguanyl hydrazones of di-phenyl di-aldehydes and di-phenyl di-ketones of claim 1, comprising reacting the corresponding di-phenyl di-aldehyde or di-phenyl di-ketone with an amino guanidine and recovering the bilateral condensation product formed.

5. A process for the production of the di-guanyl hydrazones of di-phenyl aldehydes and di-phenyl ketones of claim 1, comprising reacting a di-thiosemicarbazone of the corresponding di-phenyl di-aldehyde or di-phenyl di-ketone with ammonia or an amine in the presence of a heavy metal salt, and recovering the di-guanyl hydrazone formed. 20
6. A process for the production of the di-guanyl hydrazones of di-phenyl di-aldehydes and di-phenyl di-ketones of claim 1, comprising reacting the corresponding di-hydrazone of a di-phenyl di-aldehyde or di-phenyl di-ketone with a cyanamide and recovering the di-guanyl hydrazone formed. 25
7. A process for the production of the di-guanyl hydrazones of di-phenyl di-aldehydes and di-phenyl di-ketones of claim 1, comprising reacting a guanyl hydrazone of a hydroxy benzaldehyde or hydroxy phenyl ketone with a di-halogeno alkane in the presence of an alkali metal alkoxide and recovering the di-guanyl hydrazone formed.
8. A process for the production of di-guanyl hydrazones of di-phenyl di-ketones substantially as described in any of the foregoing Examples.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1957.
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